Remarks

Claims 1-6 are currently pending in the subject application. By this Amendment, claims 1, 2, 4 and 6 have been amended. Support for the claim amendments can be found throughout the subject specification including, for example, at page 2, line 19 (for the recitation that the product is less than 12 kDa). No new matter has been added by this amendment. Accordingly, claims 1-6 are currently before the Examiner for consideration.

The amendments to the claims have been made in an effort to lend greater clarity to the claimed subject matter and to expedite prosecution by focusing the claims on allowable subject matter. These amendments should not be taken to indicate the applicants' agreement with, or acquiescence to, the rejections of record. Favorable consideration of the claims now presented, in view of the remarks and amendments set forth herein, is earnestly solicited.

Initially, it is stated in the Office Action that status of the parent case should be updated. By this Amendment, the applicants have amended the Cross-Reference to a Related Application section of the subject application to note that the parent case (Serial No. 09/889,252) is now abandoned.

Claims 1-6 have been rejected under 35 U.S.C. §112, second paragraph. By this Amendment, the applicants have amended claims 1, 2, 4 and 6. These amendments have been made to lend greater clarity to the claimed subject matter. The applicants appreciate the Examiner's careful review of the claims as well as her helpful suggestions. The amendments set forth herein are consistent with the Examiner's suggestions and are believed to address the issues raised by the Examiner. The applicants respectfully submit that the metes and bounds of the amended claims are clearly discernable to those skilled in the art. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection under 35 U.S.C. §112, second paragraph.

Claims 1 and 4-6 have been rejected under 35 U.S.C. §103(a) as obvious over WO 95/12615. These claims are drawn to a purified product having a defined size and biological activity, and its use to treat inflammation. The applicants respectfully traverse this grounds of rejection because WO '615 does not teach or suggest a purified product having the physical properties and the advantageous characteristics of the product claimed by the current applicants.

The virtually infinite number of compounds produced by microbes, plants and animals provide a vast universe in which to search for new compounds (natural products) with beneficial functions. One potential source of useful natural products is the hookworm. The hookworm, like other animals (and even unicellular microbes), produces an enormous array of compounds. Finding and purifying a useful natural product from the hookworm is much like the proverbial search for the needle in the haystack. Thus, to find a unique needle with a useful activity is truly a great achievement. This is what the current applicants have done. The unique and advantageous contribution of the subject invention is the identification of an excretory-secretory product from *Necator Americanus*, that is less than 12 kDa, induces apoptosis in reactive T-cells, and can be used for the treatment of inflammation and cancer. The applicants respectfully submit that WO '615 provides no teaching or suggestion of a product having these unique and advantageous properties.

It is a basic premise of patent law that, in order to anticipate, a single prior art reference must disclose within its four corners, each and every element of the claimed invention. In *Lindemann v. American Hoist and Derrick Co.*, 221 USPQ 481 (Fed. Cir. 1984), the court stated:

> Anticipation requires the presence in a single prior art reference, disclosure of each and every element of the claimed invention, arranged as in the claim. *Connell v. Sears Roebuck and Co.*, 722 F.2d 1542, 220 USPQ 193 (Fed. Cir. 1983); *SSIH Equip. S.A. v. USITC*, 718 F.2d 365, 216 USPQ 678 (Fed. Cir. 1983). In deciding the issue of anticipation, the [examiner] must identify the elements of the claims, determine their meaning in light of the specification and prosecution history, and identify corresponding elements disclosed in the allegedly anticipating reference. *SSIH, supra*; *Kalman [v. Kimberly-Clarke*, 713 F.2d 760, 218 USPQ 781 (Fed. Cir. 1983)] (emphasis added). 221 USPQ at 485.

WO '615 only mentions a crude preparation from *Necatór americanus* that is an "antihaemostatic agent." Thus, WO '615 does not disclose any purified product, and certainly does not disclose a purified product that is apoptotic, less than 12 kDa, and can be used to treat cancer and inflammation. Thus, in accordance with long-established legal precedent, an anticipation rejection is not proper.

The WO '615 reference suggests that the composition described therein could be used to treat thrombotic disorders. Thrombosis is the formation of a blood clot (or "thrombus") in a blood vessel. In marked contrast, inflammation is a localized, bodily response to injury or irritation, often

characterized by pain, swelling, redness, and even loss of function. WO '615 discloses a composition that interrupts the clotting cascade by inhibiting Factor Xa activity (see pp.8-9 of WO '615). Factor Xa is produced by the liver and is a primary factor of the clotting cascade. In contrast, the present invention claims a product that induces aptotosis and can be used to treat inflammation. Thrombosis does not necessarily occur as a result of inflammation; nor does inflammation necessarily occur as a result of thrombosis. The treatment of thrombosis disclosed by WO '615 occurs as a result of an entirely distinct physiological mechanism compared to the apoptotic effect of the current invention. Thus, there is no basis for equating the treatment of thrombosis with the treatment of inflammation.

The Office Action suggests that the claimed compounds "inherently" have the properties of the WO '615 composition (or vice versa). Under the Patent Laws, a prior art rejection based on inherency is proper only if the prior art necessarily resulted in the claimed subject matter. *In re King*, 801 F.2d 1324, 1326, 231 USPQ 136, 138 (Fed. Cir. 1986). Further,

> The doctrine of inherency is available only when the prior inherent event can be established as a certainty. That an event may result from a given set of circumstances is not sufficient to establish anticipation....A prior inherent event cannot be established based on speculation, or where a doubt exists (emphasis added). *Ethyl Molded Product Co. v. Betts Package Inc.*, 9 USPQ2d 1001, 1032-33 (E.D. KY 1988).

It cannot reasonably be stated that treatment of thrombotic disorders necessarily treats inflammation. Thus, the Office Action falls far short of meeting the legal requirements for basing an anticipation rejection on inherency.

The purpose of 35 U.S.C. §102 is to prevent the granting of a patent which would remove from the public something that has already been placed in the public domain. It is clear from the foregoing remarks that, at the time of the subject invention, the public was not in possession of the applicants' unique compounds, nor was the skilled artisan in possession of a method of using these compounds for the treatment of inflammation. Accordingly, the applicants respectfully request reconsideration and withdrawal of the prior art rejection of claims 1 and 4-6 under 35 U.S.C. §102(b).

With regard to the issue of obviousness, nothing in the WO '615 reference would have led the skilled artisan to the advantageous materials and methods claimed by the current applicants. As noted above, no physical or functional similarities exist between the current applicants' purified product and the composition described in the WO '615 reference.

The separation profile of the excretory-secretory products of *Necator americanus* is indicated on the attached graph. The factor Xa inhibitor described in WO95/12615 is shown, as is the glutathione-s-transferase product disclosed by Brophy *et al.* It is clear from this chart that the products disclosed in the prior art are distinct from, and unrelated to, the product now claimed. The distinction is evident not only on the basis of the molecular weight of the products, but also in terms of the activity of each product.

A finding of obviousness is proper only when the prior art contains a suggestion or teaching of the claimed invention. Here, it is only the applicants' disclosure that provides such a teaching, and the applicants' disclosure cannot be used to reconstruct the prior art for a rejection under 35 U.S.C. §103. This was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969):

> The Court must be ever alert not to read obviousness into an invention on the basis of the applicant's own statements; that is we must review the prior art without reading into that art appellant's teachings. *In re Murray*, 46 CCPA 905, 268 F.2d 226, 112 USPQ 364 (1959); *In re Sprock*, 49 CCPA 1039, 301 F.2d 686, 133 USPQ 360 (1962). The issue, then, is whether the teachings of the prior art would, in and of themselves and without the benefits of appellant's disclosure, make the invention as a whole, obvious. *In re Leonor*, 55 CCPA 1198, 395 F.2d 801, 158 USPQ 20 (1968). (Emphasis in original)

The mere fact that the purported prior art could have been modified or applied in a manner to yield applicant's invention would not have made the modification or application obvious unless the prior art suggested the desirability of the modification. *In re Gordon*, 221 USPQ 1125, 1127 (Fed. Cir. 1984). Moreover, as expressed by the CAFC, to support a 103 rejection, "[b]oth the suggestion and the expectation of success must be founded in the prior art . . . ." *In re Dow Chemical Co., supra* at 1531. In the WO '615 reference, one finds neither. Accordingly, the applicants respectfully

request reconsideration and withdrawal of the rejection of claims 1 and 4-6 as obvious in view of the WO '615 reference.

Claims 1 and 4-6 have been rejected under 35 U.S.C. §102(b) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Brophy *et al.* The applicants respectfully traverse this ground for rejection because Brophy *et al.* do not disclose or suggest the current applicants' product, or its use in treating inflammation.

Brophy *et al.* discloses products that are glutathione-s-transferases. As noted above, the attached chart shows that the fraction from *Nectar americanus* that has glutathione-s-transferase activity is clearly distinct from the product claimed by the current applicants.

There is no reason to believe that there is any similarity between the currently-claimed product and the Brophy *et al.* compounds. The claimed compounds do not have glutathione-S-transferase activity. Also, there is no reason to believe that the Brophy *et al.* products are capable of inducing apoptosis in reactive T-cells. Nor do Brophy *et al.* suggest that their compounds could be used in the treatment of inflammation. If, upon careful review of the Brophy *et al.* article the Examiner remains of the opinion that Brophy *et al.* teach the treatment of inflammation, the applicants respectfully request that the specific location of that teaching be identified.

As noted above, for an anticipation rejection to be proper, a single prior art reference must disclose, within its four corners, each and every element of the claimed invention. In *Dewey & Almy Chem. Co. v. Mimex Co.*, Judge Learned Hand wrote:

> No doctrine of the patent law is better established than that a prior patent . . . to be an anticipation must bear within its four corners adequate directions for the practice [of the subsequent invention] . . . if the earlier disclosure offers no more than a starting point . . . if it does not inform the art without more how to practice the new invention, it has not correspondingly enriched the store of common knowledge, and it is not an anticipation. 124 F.2d 986, 990; 52 USPQ 138 (2nd Cir. 1942).

In the current case, Brophy *et al.* do not disclose, explicitly or inherently, an excretory-secretory product that is less than 12 kDa and is capable of promoting apoptosis, nor do they disclose any method for treating inflammation. Therefore, in accordance with applicable legal precedent, as discussed above, the applicants respectfully submit that the anticipation rejection of claims 1 and 4-6 should be withdrawn upon reconsideration.

J:\sh-resp\gje\gje2\GJE-73D1-2Amend.doc\DNB/la

Also, with regard to obviousness, because Brophy *et al.* describe an entirely different product than what is being claimed by the current applicants, there is no teaching provided by Brophy *et al.* that would, or could, lead the skilled artisan to the particular advantageous materials, or uses, claimed by the current applicants. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 4-6 as being obvious under 35 U.S.C. §103 in view of Brophy *et al.*

Claims 1 and 4-6 have been rejected under 35 U.S.C. §102(e) as anticipated by or, in the alternative, under 35 U.S.C. §103(a) as obvious over Vlasuk *et al.* The applicants respectfully traverse this grounds for rejection because Vlasuk *et al.* do not disclose or suggest the material claimed by the current applicants, or its use to treat inflammation or cancer.

As noted above, an anticipation rejection is proper only when a single reference discloses all of the elements of the claimed invention. Vlasuk *et al.* only disclose an anticoagulant protein obtained from nematodes. There is no disclosure of the applicants' material that is less than 12 kDa and has apoptotic properties. Furthermore, Vlasuk *et al.* do not disclose that their product can be used to treat cancer. Cancer is referred to in column 38, line 15 of the Vlasuk *et al.* reference as a condition that causes abnormal thrombosis; thus, the protein disclosed in Vlasuk *et al.* may be used to treat the thrombosis, but not the cancer.

Because the Vlasuk *et al.* reference does not disclose, within its four corners, the subject matter as claimed in the current application, an anticipation rejection under 35 U.S.C. §102 is not proper. Furthermore, there is nothing in the Vlasuk *et al.* reference that would suggest the characteristics, or even the existence, of a hookworm compound having anti-inflammatory or anti-cancer activity. Without such a teaching the current applicants' claims to an excretory-secretory product with anti-inflammatory and anti-cancer activity cannot be obvious. Accordingly, the applicants respectfully request reconsideration and withdrawal of the prior art rejections based on the Vlasuk *et al.* reference.

Claims 1 and 4-6 have been rejected under 35 U.S.C. §103(a) as being unpatentable over WO 95/12615 and Brophy *et al.*, in view of Kalinkovich *et al.* The shortcomings of the WO '615 reference and the Brophy *et al.* reference have been discussed above. The Kalinkovich citation does

not cure the defects of the primary references, or otherwise provide the necessary teachings to enable or even motivate a person skilled in the art to identify an excretory-secretory product that is less than 12 kDa and induces apoptosis.

The Office Action notes that T-cell apototosis has been observed in individuals infected with *Necator americanus*. However, such an observation falls far short of providing the necessary teachings to arrive at the conclusion that the applicants' claims to a specific unique product are obvious. The applicants are claiming a specific purified material, and its use to treat inflammation and cancer. The fact that apoptotic cells are found in hookworm-infected people does not establish, or even imply, that hookworm products have apoptotic effects. Apoptotoic cell death is a natural progression of many immune responses; therefore, apoptosis in infected individuals may well be the result of activation of the immune system rather than any effect of a hookworm product. Clearly, this teaching does not point to an excretory-secretory product, as currently claimed, with the specific physical properties and advantageous characteristics as identified herein.

As noted above, for an obviousness rejection to be proper, the prior art must provide motivation that leads to the claimed invention, and a reasonable expectation of success. An assertion of obviousness with the required suggestion or expectation of success in the prior art is tantamount to using the applicants' disclosure to reconstruct the prior art to arrive at the subject invention. Hindsight reconstruction of the prior art cannot support a §103 rejection, as was specifically recognized by the CCPA in *In re Sponnoble*, 56 CCPA 823, 160 USPQ 237, 243 (1969).

In the current case, the cited references provide no reasonable motivation to even look at hookworms as a source for anti-inflammatory or anti-cancer agents. Certainly there is no teaching of the particular excretory-secretory product claimed by the current applicants. Accordingly, the applicants respectfully request reconsideration and withdrawal of the rejection of claims 1 and 4-6 under 35 U.S.C. §103 based on WO '615, Brophy *et al.* and Kalinkovich.

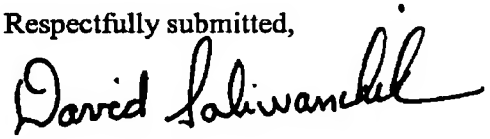
In view of the foregoing remarks, and the amendments to the claims, the applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

J:\sh-resp\gje\gje2\GJE-73D1-2Amend.doc\DNB/la

The Commissioner is hereby authorized to charge any fees under 37 CFR §§§1.16, 1.17, or 1.492 as required by this paper to Deposit Account No. 19-0065.

The applicants also invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephone interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

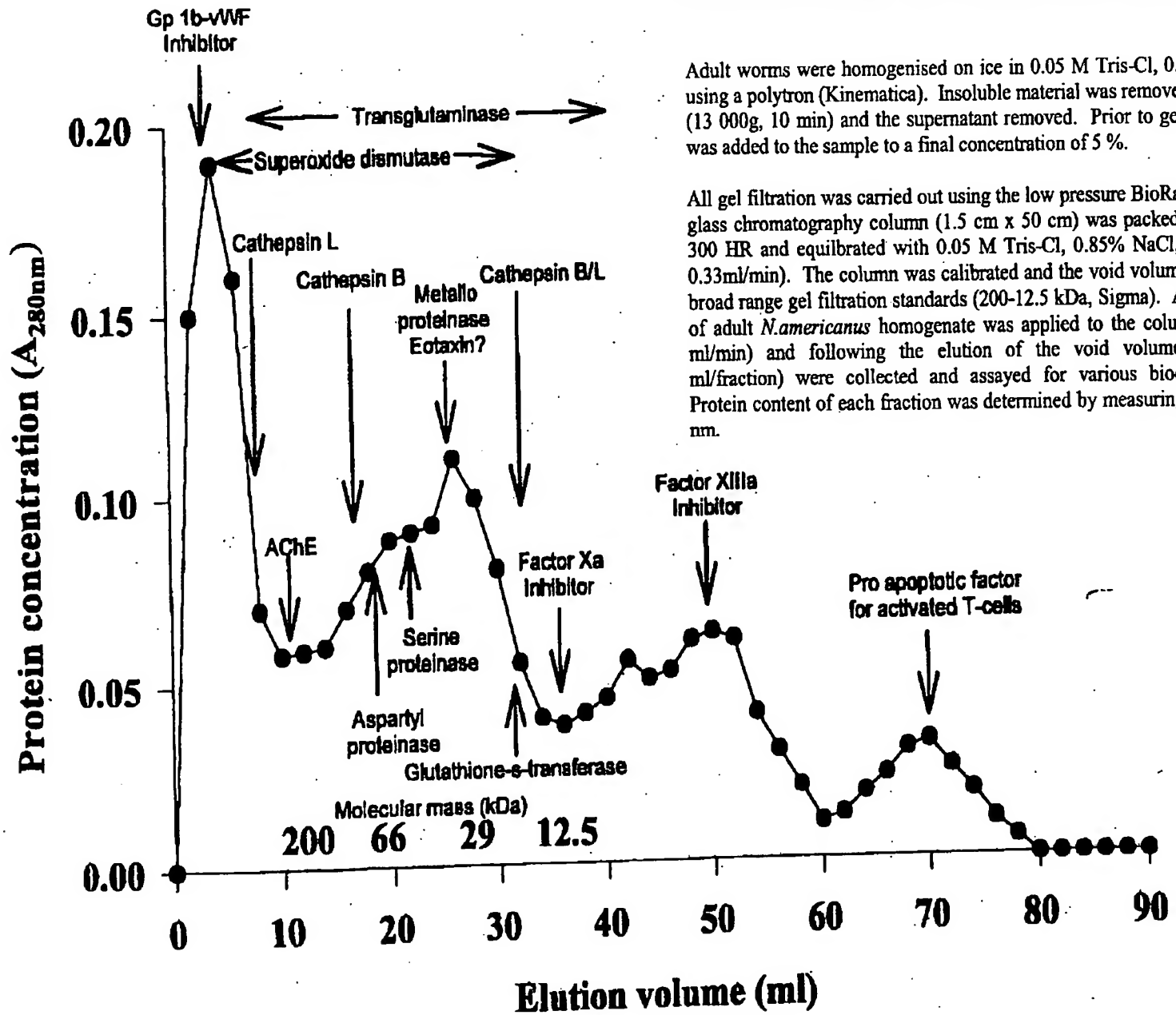


David R. Saliwanchik
Patent Attorney
Registration No. 31,794
Phone: 352-375-8100
Fax No.: 352-372-5800
Address: 2421 N.W. 41st Street, Suite A-1
Gainesville, FL 32606-6669

DRS/la

Attachment: Protein concentration graph

S-300HR GEL FILTRATION OF *N.AMERICANUS* HOMOGENATE



Adult worms were homogenised on ice in 0.05 M Tris-Cl, 0.85% NaCl, pH 7.5 using a polytron (Kinematica). Insoluble material was removed by centrifugation (13 000g, 10 min) and the supernatant removed. Prior to gel filtration glycerol was added to the sample to a final concentration of 5 %.

All gel filtration was carried out using the low pressure BioRad Econosystem. A glass chromatography column (1.5 cm x 50 cm) was packed with Sephacryl S-300 HR and equilbrated with 0.05 M Tris-Cl, 0.85% NaCl, pH 7.5 (flow rate 0.33ml/min). The column was calibrated and the void volume determined using broad range gel filtration standards (200-12.5 kDa, Sigma). Approximately 2 ml of adult *N.americanus* homogenate was applied to the column (flow rate 0.33 ml/min) and following the elution of the void volume, 45 fractions (2 ml/fraction) were collected and assayed for various biochemical activities. Protein content of each fraction was determined by measuring absorbance at 280 nm.